Amendments to the Specification

Please replace the passage from the beginning of page 20 to the end of page 57 by the following amended passage:

Example 1: Bi-layered Tablet (Wet Granulation)

[0078] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate and pseudoephedrine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Sustained release)		
Guaifenesin	600.0	510.6
~~Methocel~~ METHOCEL K15M	100.0	85.1
Silicified Microcrystalline Cellulose	50	42.6
~~Eudragit~~ EUDRAGIT NE	42	35.7
Magnesium Stearate	8.0	6.8
Layer 2 (Sustained release)		

Codeine Phosphate	30.0	25.5
Pseudoephedrine HCl	120.0	102.1
Microcrystalline Cellulose (PH 102)	45.0	38.3
~~Eudragit~~ EUDRAGIT NE	15.0	12.8
~~Methocel~~ METHOCEL K4M Premium	140.0	119.1
Stearic Acid	20.0	17.0
Magnesium Stearate	5.0	4.3
Total	**1175.0**	**1000.0**

Procedure:

[0079] (a) Sustained release layer #1: Mix the guaifenesin, ~~Methocel~~ METHOCEL ®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Dry the granulation until the LOD (weight loss on drying) is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0080] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, pseudoephedrine HCl, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Add the ~~Methocel~~ METHOCEL ®K4M to the granulator and post mix for 5 minutes.

Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0081] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 800 mgs and layer #2 is 375 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 2: Bi-layered Tablet (Wet Granulation)

[0082] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in an immediate release layer and codeine phosphate and pseudoephedrine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Immediate release)		
Promethazine HCl	25.0	37.0
Silicified Microcrystalline Cellulose	111.0	164.3
~~Povidone~~ POVIDONE	3.0	4.4
Croscarmellose Sodium	10.0	14.8

Magnesium Stearate	1.0	1.5
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	44.4
Pseudoephedrine HCl	120.0	177.6
Microcrystalline Cellulose (PH 102)	30.0	44.4
Dicalcium Phosphate	100.0	148.0
~~Povidone~~ POVIDONE	15.0	22.2
~~Methocel~~ METHOCEL K4M Premium	205.0	303.4
Stearic Acid	20.0	29.6
Magnesium Stearate	5.0	7.4
Total	**675.0**	**1000.0**

Procedure:

[0083] (a) Immediate release layer #1: Mix the promethazine HCl, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (3.0 gms ~~povidone~~ POVIDONE in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V

shaped blender and mix for 3 minutes.

[0084] (b) Sustained release layer #2: Mix the codeine phosphate, pseudoephedrine HCl, microcrystalline cellulose PH 102, dicalcium phosphate, ~~Methocel~~ METHOCEL K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (15.0 gms ~~povidone~~ POVIDONE in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0085] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 150 mgs and layer #2 is 525 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 3: Bi-layered Tablet (Wet Granulation)

[0086] A bi-layered tablet in accordance with the present invention which comprises phenylepherine hydrochloride and carbinoxamine maleate in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Sustained release)		

Phenylepherine HCl	75.0	185.2
Carbinoxamine Maleate	8.0	19.8
~~Methocel~~ METHOCEL K4M	59.0	145.7
Silicified Microcrystalline Cellulose	30.0	74.1
~~Eudragit~~ EUDRAGIT NE	15.0	37.0
Magnesium Stearate	3.0	7.4
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	74.1
Microcrystalline Cellulose (PH 102)	45.0	111.1
~~Eudragit~~ EUDRAGIT NE	15.0	37.0
~~Methocel~~ METHOCEL K4M Premium	100.0	246.9
Stearic Acid	20.0	49.4
Magnesium Stearate	5.0	12.3
Total	**405.0**	**1000.0**

Procedure:

[0087] (a) Sustained release layer #1: Mix the phenylepherine HCl, carbinoxamine maleate, ~~Methocel~~ METHOCEL ®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0088] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Add the ~~Methocel~~ METHOCEL ®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0089] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 190 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 4: Bi-layered Tablet (Wet Granulation)

[0090] A bi-layered tablet in accordance with the present invention which comprises pseudoephedrine hydrochloride and chlorpheniramine maleate in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Sustained release)		
Pseudoephedrine HCl	120.0	253.2
Chlorpheniramine Maleate	12.0	25.3
~~Methocel~~ METHOCEL K4M	70.0	147.7
Silicified Microcrystalline Cellulose	35.0	73.9
~~Eudragit~~ EUDRAGIT NE	20.0	42.2
Magnesium Stearate	3.0	6.3
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	63.3
Microcrystalline Cellulose (PH 102)	45.0	95.0

~~Eudragit~~ EUDRAGIT NE	15.0	31.7
~~Methocel~~ METHOCEL K4M Premium	100.0	211.0
Stearic Acid	20.0	42.2
Magnesium Stearate	5.0	10.6
Total	**475.0**	**1000.0**

Procedure:

[0091] (a) Sustained release layer #1: Mix the pseudoephedrine HCl, chlorpheniramine maleate, ~~Methocel~~ METHOCEL®K4M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0092] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Add the ~~Methocel~~ METHOCEL ®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0093] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer

#1 is 260 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 5: Bi-layered Tablet (Wet Granulation)

[0094] A bi-layered tablet in accordance with the present invention which comprises carbinoxamine maleate in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Sustained release)		
Carbinoxamine Maleate	8.0	19.3
Lactose Monohydrate	61.0	147.0
~~Methocel~~ METHOCEL K4M	70.0	168.7
Silicified Microcrystalline Cellulose	39.0	94.0
~~Eudragit~~ EUDRAGIT NE	20.0	48.2
Magnesium Stearate	2.0	4.82
Layer 2 (Sustained release)		

Codeine Phosphate	30.0	72.3
Microcrystalline Cellulose (PH 102)	45.0	108.5
~~Eudragit~~ EUDRAGIT NE	15.0	36.2
~~Methocel~~ METHOCEL K4M Premium	100.0	241.0
Stearic Acid	20.0	48.2
Magnesium Stearate	5.0	12.1
Total	**415.0**	**1000.0**

Procedure:

[0095] (a) Sustained release layer #1: Mix the carbinoxamine maleate, ~~Methocel~~ METHOCEL ®K4M, lactose monohydrate and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0096] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, microcrystalline cellulose PH 102, and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Add the ~~Methocel~~ METHOCEL ®K4M to the granulator and post mix for 5 minutes. Dry the

granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0097] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 200 mgs and layer #2 is 215 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 6: Bi-layered Tablet (Direct Compression)

[0098] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride (longer half-life drug) in an immediate release layer and codeine phosphate (shorter half-life drug) in a sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mg)**	**Weight/1kg batch (in grams)**
Layer 1 (Immediate release)		
Promethazine HCl	25	45.5
Silicified Microcrystalline Cellulose	114.0	207.5
Sodium Starch Glycolate	10.0	18.2
Magnesium Stearate	1.0	1.8

Layer 2 (Sustained release)		
Codeine Phosphate	60.0	109.2
Lactose Monohydrate	50.0	91.0
Dicalcium Phosphate	50.0	91.0
~~Kollidon~~ KOLLIDON SR	220.0	400.4
Stearic acid	15.0	27.3
Magnesium Stearate	5.0	9.1
Total	**550.0**	**1000.0**

Procedure:

[0099] (a) Immediate release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the promethazine hydrochloride, microcrystalline cellulose and sodium starch glycolate for 20 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0100] (b) Sustained release layer #2: Blend the codeine phosphate, lactose monohydrate, dicalcium phosphate and ~~Kollidon~~ KOLLIDON® SR for 20 minutes. Add stearic acid and magnesium stearate to the above blend and mix for an additional time of three minutes.

[0101] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer #1 is 150 mgs and the sustained release layer #2 is 400 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 7: Bi-layered Tablet (Wet Granulation):

[0102] A bi-layered tablet in accordance with the present invention which comprises pseudoephedrine tannate and chlorpheniramine tannate in an immediate release layer and codeine phosphate in a sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Immediate release)		
Pseudoephedrine Tannate	60.0	85.7
Chlorpheniramine Tannate	8.0	11.4
Silicified Microcrystalline Cellulose	108.0	154.3
~~Povidone~~ POVIDONE	3.0	4.3
Croscarmellose Sodium	10.0	14.3
Magnesium Stearate	1.0	1.4
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	42.9
Microcrystalline Cellulose (PH 102)	30.0	42.9

Lactose Monohydrate	100.0	142.9
Dicalcium Phosphate	100.0	142.9
~~Povidone~~ POVIDONE	15.0	21.4
~~Methocel~~ METHOCEL K4M Premium	210.0	300.0
Stearic Acid	20.0	28.6
Magnesium Stearate	5.0	7.1
Total	**700.0**	**1000.0**

Procedure:

[0103] (a) Immediate release layer #1: Mix the pseudoephedrine tannate, chlorpheniramine tannate, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (3.0 gms ~~povidone~~ POVIDONE in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0104] (b) Sustained release layer #2: Mix the codeine phosphate, microcrystalline cellulose PH 102, lactose monohydrate, dicalcium phosphate, ~~Methocel~~ METHOCEL K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (15.0 gms ~~povidone~~ POVIDONE in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add

the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0105] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 190 mgs and layer #2 is 510 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 8: Bi-layered Tablet (Wet Granulation):

[0106] A bi-layered tablet in accordance with the present invention which comprises promethazine hydrochloride in an immediate release layer and codeine phosphate and phenylepherine hydrochloride in a sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Immediate release)		
Promethazine HCl	25	55.5
Silicified Microcrystalline Cellulose	86.0	190.0
~~Povidone~~ POVIDONE	3.0	6.7
Croscarmellose Sodium	10.0	22.2
Magnesium Stearate	1.0	2.2

Layer 2 (Sustained release)		
Codeine Phosphate	30.0	66.6
Phenylepherine HCl	75.0	166.5
Microcrystalline Cellulose (PH 102)	30.0	66.6
Dicalcium Phosphate	30.0	66.6
~~Povidone~~ POVIDONE	15.0	33.3
~~Methocel~~ METHOCEL K4M Premium	120.0	266.4
Stearic Acid	20.0	44.4
Magnesium Stearate	5.0	11.1
Total	**450.0**	**1000.0**

Procedure:

[0107] (a) Immediate release layer #1: Mix the promethazine hydrochloride, silicified microcrystalline cellulose and croscarmellose sodium, in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (3.0 gms ~~povidone~~ POVIDONE in 10.0 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0108] (b) Sustained release layer #2: Mix the codeine phosphate, phenylepherine HCl,

microcrystalline cellulose PH 102, dicalcium phosphate, ~~Methocel~~ METHOCEL K4M Premium and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (15.0 gms ~~povidone~~ POVIDONE in 50.0 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0109] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 125 mgs and layer #2 is 325 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 9: Bi-layered Tablet (Direct Compression)

[0110] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mg)**	**Weight/1kg batch (in grams)**
Layer 1 (Sustained release)		
Guaifenesin	600.0	499.8

~~Methocel~~ METHOCEL K15M	200.0	166.6
Silicified Microcrystalline Cellulose	72	60.0
Magnesium Stearate	8.0	6.7
Layer 2 (Sustained release)		
Codeine Phosphate	60.0	50.0
Lactose Monohydrate	35.0	29.2
Dicalcium Phosphate	35.0	29.2
~~Kollidon~~ KOLLIDON SR	170.0	141.6
Stearic acid	15.0	12.5
Magnesium Stearate	5.0	4.2
Total	**1200.0**	**1000.0**

Procedure:

[0111] (a) Sustained release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the guaifenesin, ~~Methocel~~ METHOCEL ® K15M and silicified microcrystalline cellulose for 25 minutes. Add magnesium stearate to the above blend and mix for an additional time of three minutes.

[0112] (b) Sustained release layer #2: Blend the codeine phosphate, lactose monohydrate, dicalcium phosphate and ~~Kollidon~~ KOLLIDON ® SR for 20 minutes. Add stearic acid and

magnesium stearate to the above blend and mix for an additional time of three minutes.

[0113] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 880 mgs and layer #2 is 320 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 10: Bi-layered Tablet (Wet Granulation)

[0114] A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate and phenylepherine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Sustained release)		
Guaifenesin	600.0	558.0
~~Methocel~~ METHOCEL K15M	100.0	93.0
Silicified Microcrystalline Cellulose	50	46.5
~~Eudragit~~ EUDRAGIT NE	42	39.1
Magnesium Stearate	8.0	7.4

Layer 2 (Sustained release)		
Codeine Phosphate	30.0	27.9
Phenylepherine HCl	60.0	55.8
Microcrystalline Cellulose (PH 102)	45.0	41.9
~~Eudragit~~ EUDRAGIT NE	15.0	14.0
~~Methocel~~ METHOCEL K4M Premium	100.0	93.0
Stearic Acid	20.0	18.6
Magnesium Stearate	5.0	4.7
Total	**1075.0**	**1000.0**

Procedure:

[0115] (a) Sustained release layer #1: Mix the guaifenesin, ~~Methocel~~ METHOCEL ®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0116] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, phenylepherine HCl, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above

blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Add the ~~Methocel~~ METHOCEL ®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0%. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

controlled release layer(s) of a multi-layered (e.g., bi-layered) tablet.

[0117] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 800 mgs and layer #2 is 275 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 11: Bi-layered Tablet (Wet Granulation)

A bi-layered tablet in accordance with the present invention which comprises guaifenesin in a first sustained release layer and codeine phosphate and phenylepherine hydrochloride in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Sustained release)		
Guaifenesin	1000.0	635.0
~~Methocel~~ METHOCEL K15M	200.0	127.0

Silicified Microcrystalline Cellulose	40.0	25.4
~~Eudragit~~ EUDRAGIT NE	50.0	31.8
Magnesium Stearate	10.0	6.4
Layer 2 (Sustained release)		
Codeine Phosphate	30.0	19.1
Phenylepherine HCl	60.0	38.1
Microcrystalline Cellulose (PH 102)	45.0	28.6
~~Eudragit~~ EUDRAGIT NE	15.0	9.5
~~Methocel~~ METHOCEL K4M Premium	100.0	63.5
Stearic Acid	20.0	12.7
Magnesium Stearate	5.0	3.2
Total	**1575.0**	**1000.0**

Procedure:

[0118] (a) Sustained release layer #1: Mix the guaifenesin, ~~Methocel~~ METHOCEL ®K15M and silicified microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0119] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Mix the codeine phosphate, phenylepherine HCl, microcrystalline cellulose PH 102, dicalcium phosphate and stearic acid in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a ~~Eudragit~~ EUDRAGIT ® NE (30 %). Add the ~~Methocel~~ METHOCEL ®K4M to the granulator and post mix for 5 minutes. Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0120] controlled release layer(s) of a multi-layered (e.g., bi-layered) tablet Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 1300 mgs and layer #2 is 275 mgs. Capsules may be manufactured by filling the same proportions into capsules.

Example 12: Bi-layered Tablet (Direct Compression)

[0121] A bi-layered tablet in accordance with the present invention which comprises codeine phosphate in a first sustained release layer and phenylepherine hydrochloride and chlorpheniramine maleate in a second sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mg)**	**Weight/1kg batch (in grams)**
Layer 1 (Sustained release)		
Codeine Phosphate	30	54.5
Methocel K4M	50	90.9
Silicified Microcrystalline Cellulose	100.0	181.8
Sodium Starch Glycolate	10.0	18.2
Magnesium Stearate	1.0	1.8
Layer 2 (Sustained release)		
Phenylepherine HCl	60	109
Chlorpheniramine Maleate	8.0	14.5
Lactose Monohydrate	50.0	90.9

Dicalcium Phosphate	50.0	90.9
~~Methocel~~ METHOCEL K4M	181.0	329.1
Stearic acid	15.0	27.3
Magnesium Stearate	5.0	9.1
Total	**550.0**	**1000.0**

Procedure:

[0122] (a) Sustained release Layer #1: Screen all ingredients through a USP sieve size # 30. Preblend a portion of the ~~Kollidon~~ KOLLIDON SR (145 gms) and all the codeine phosphate for 15 minutes. Add lactose monohydrate (90.9 gms) and dicalcium phosphate (90.9 gms) to the above preblend and mix for an additional 20 minutes. Add stearic acid (27.3 gms) and magnesium stearate (9.1 gms) to the above blend and mix for three minutes.

[0123] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Preblend a portion of the ~~Kollidon~~ KOLLIDON SR (145 gms) and all the chlorpheniramine maleate (14.5 gms) for 15 minutes. Add the remaining ~~Kollidon~~ KOLLIDON SR (313.2 gms), phenylepherine hydrochloride (36.4 gms), lactose monohydrate (90.9 gms) and dicalcium phosphate (90.9 gms) to the above preblend and mix for an additional 20 minutes. Add stearic acid (27.3 gms) and magnesium stearate (9.1 gms) to the above blend and mix for three minutes.

[0124] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 150 mgs and the sustained release layer is 400 mgs.

Example 13: Bi-layered Tablet (Direct Compression)

[0125] By using the process described in Example 12, a bi-layered tablet which contains codeine phosphate in an immediate release layer and codeine phosphate, phenylepherine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using direct compression:

Ingredients	**Weight/tablet (mgs)**
Layer 1 (Immediate Release)	
Codeine Phosphate	10
Silicified Microcrystalline Cellulose	133.5
Sodium Starch Glycolate	15
Magnesium Stearate	1.5
Layer 2 (Sustained Release)	
Codeine Phosphate	40
Phenylepherine HCl	50
Chlorpheniramine Maleate	8
Lactose Monohydrate	50

Dicalcium Phosphate	50
~~Kollidon~~ KOLLIDON SR	252
Stearic Acid	15
Magnesium Stearate	5
Total	**620**

Example 14: Bi-layered Tablet (Wet Granulation)

[0126] A bi-layered tablet in accordance with the present invention which comprises codeine phosphate in an immediate release layer and codeine phosphate, pseudoephedrine hydrochloride and chlorpheniramine maleate in a sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Immediate release)		
Codeine Phosphate	10.0	11.9
Silicified Microcrystalline Cellulose	111.0	158.6
~~Povidone~~ POVIDONE	3.0	4.3
Croscarmellose Sodium	10.0	14.3

Magnesium Stearate	1.0	1.4
Layer 2 (Sustained release)		
Codeine Phosphate	30	35.7
Pseudoephedrine HCl	60.0	85.7
Chlorpheniramine Maleate	8.0	11.4
Microcrystalline Cellulose (PH 102)	30.0	42.9
Lactose Monohydrate	100.0	142.9
Dicalcium Phosphate	100.0	142.9
~~Povidone~~ POVIDONE	15.0	21.4
~~Methocel~~ METHOCEL K4M Premium	212.0	302.9
Stearic Acid	20.0	28.6
Magnesium Stearate	5.0	7.1
Total	**700.0**	**1012.0**

Procedure:

[0127] (a) Immediate release layer #1: Screen all ingredients through a USP sieve size # 30. Blend the codeine phosphate (11.9 grams), silicified microcrystalline cellulose (158.6 grams), and croscarmellose sodium in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (4.3 gms ~~povidone~~ POVIDONE in 14.3 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a

USP sieve size # 14. Add granules and the prescreened magnesium stearate (1.4 gms) to the above blend and mix for 3 minutes.

[0128] (b) Sustained release layer #2: Screen all ingredients through a USP sieve size # 30. Blend the pseudoephedrine hydrochloride (87.5 gms), chlorpheniramine maleate (11.4 gms), codeine phosphate (37.5 gms), microcrystalline cellulose PH 102 (42.9 gms), lactose monohydrate (142.9 gms), dicalcium phosphate (142.9gms), ~~Methocel~~ METHOCEL K4M Premium (302.9 gms) and stearic acid (28.6 gms) in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (21.4 gms ~~povidone~~ POVIDONE in 71.3 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add granules and the prescreened magnesium stearate (7.1 gms) to the above blend and mix for 3 minutes.

[0129] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet the immediate release layer is 150 mgs and the sustained release layer is 550 mgs.

Example 15: Bi-layered Tablet (Wet Granulation)

[0130] By using the process described in Example 14, a bi-layered tablet containing codeine phosphate in an immediate release layer and pseudoephedrine hydrochloride and chlorpheniramine maleate in a sustained release layer may be manufactured by using wet granulation:

Ingredients	Weight/tablet (mgs)
Layer 1 (Immediate Release)	
Codeine Phosphate	30
Silicified Microcrystalline cellulose	129.5
~~Povidone~~ POVIDONE	4
Croscarmellose sodium	15
Magnesium Stearate	1.5
Layer 2 (Sustained Release)	
Pseudoephedrine HCl	60
Chlorpheniramine Maleate	8
Microcrystalline Cellulose 102	30
Lactose Monohydrate	100
Dicalcium Phosphate	100
~~Povidone~~ POVIDONE	15
Hydroxypropylmethylcellulose	212
Stearic Acid	20

Magnesium Stearate	5
Total	**750**

[0131] The above examples illustrate how to manufacture a bi-layered tablet containing codeine phosphate in (at least) a first layer and an antihistamine and/or a decongestant and/or an expectorant in (at least) a second layer. Non-limiting examples of possible active ingredients (in addition to the antitussive morphine derivative) in an exemplary range as described in the following Table 1 can be employed depending on the specific therapeutic effect desired.

Table 1

Active ingredient	**Amount per Tablet**	**Preferred Amount per Tablet**	**OTC Daily Dosage**
ANTIHISTAMINES			
Azelastine hydrochloride	0.1 - 2.0 mg	0.125 mg	
Azatadine hydrochloride	0.1 – 4.0 mg	1 mg	
Brompheniramine maleate	0.1 – 64 mg	2-16 mg	24 mg
Dexbrompheniramine maleate	0.1 – 24 mg	3-6 mg	12 mg
Carbinoxamine maleate	0.1 – 16 mg	4 mg	
Cetirizine hydrochloride	0.1 – 40 mg	5-10 mg	
Chlorcyclizine	0.1 – 300 mg		75 mg

Chlorpheniramine maleate	0.1 – 64 mg	2-16 mg	24 mg
Chlorpheniramine polistirex	0.1 – 32 mg	4-8 mg	
Clemastine	0.1 – 12 mg	0.5-2.68 mg	
Cyproheptadine	0.1 – 16 mg	2-4 mg	
Dexchlorpheniramine maleate	0.1 – 24 mg	2 mg	12 mg
Cyproheptadine hydrochloride	0.1 – 32 mg	2-4 mg	
Diphenhydramine hydrochloride	0.1 – 300 mg	10-50 mg	300 mg
Diphenhydramine citrate	0.1 – 2000 mg		456 mg
Bromodiphenhydramine hydrochloride	0.1 – 200 mg	12.5-25 mg	
Doxylamine succinate	0.1 – 200 mg	12.5-25 mg	75 mg
Fexofenadine hydrochloride	0.1 – 720 mg	30-180 mg	
Hydroxyzine hydrochloride	0.1 – 400 mg	10-100 mg	
Hydroxyzine pamoate	0.1 – 400 mg	25-100 mg	
Loratadine	0.1 – 80 mg	1-10 mg	
Desloratadine	0.1 – 40 mg	5 mg	
Phenindamine tartrate	0.1 – 750 mg		150 mg
Pheniramine maleate	0.1 – 750 mg		150 mg
Pyrilamine maleate	0.1 – 200 mg	25 mg	200 mg
Terfenadine			
Thenyldiamine			

Thonzylamine	0.1 – 3000 mg		600 mg
Thymol			
Tripelennamine hydrochloride	0.1 – 400 mg	25-50 mg	
Triprolidine hydrochloride	0.1 – 40 mg	1.25-5 mg	10 mg
EXPECTORANT			
Guaifenesin	0.1 – 2000 mg	50-1200	2400 mg

Example 16: Bi-layered Tablet (Direct Compression and Wet Granulation)

[0132] A bi-layered tablet in accordance with the present invention which contains codeine phosphate in both an immediate release layer and a sustained release layer is illustrated as follows:

Ingredients	**Weight/tablet (mgs)**	**Weight/1kg batch (gms)**
Layer 1 (Immediate release)		
Codeine Phosphate	15.0	46.2
Silicified Microcrystalline Cellulose	73.5	226.4
Croscarmellose Sodium	10.0	30.8
Magnesium Stearate	1.5	4.6
Layer 2 (Sustained release)		
Codeine Phosphate	45.0	138.6
Microcrystalline Cellulose (PH 102)	20.0	61.6
~~Povidone~~ POVIDONE	8.0	24.6
~~Methocel~~ METHOCEL K4M Premium	150.0	462.0
Magnesium Stearate	2.0	6.2

Total	**325.0**	**1000.0**

Procedure:

[0133] (a) Immediate release layer #1: Mix the prescreened (# 30 mesh) codeine phosphate, silicified microcrystalline cellulose and croscarmellose sodium, in a V shaped blender for 20 minutes. Add prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0134] (b) Sustained release layer #2: Mix the codeine phosphate, ~~Methocel~~ METHOCEL K4M Premium and microcrystalline cellulose in a high shear mixer/granulator for 10 minutes. Granulate the above blend using a 30 % ~~povidone~~ POVIDONE solution (8.0 gms ~~povidone~~ POVIDONE in 26.7 gms purified water). Dry the granulation until the LOD is less than 2.0 %. Screen granules through a USP sieve size # 14. Add the granules and the prescreened magnesium stearate in a V shaped blender and mix for 3 minutes.

[0135] Manufacture bi-layered tablets using a rotary bi-layer tablet press where in each tablet layer #1 is 100 mgs and layer #2 is 225 mgs.

Example 17: Single layer Tablet or Capsule

[0136] A single layer tablet or a capsule in accordance with the present invention which contains codeine phosphate both in an immediate release form and in a sustained release form is illustrated as follows:

Ingredients	Amount (mg) / tablet
Codeine Phosphate Ion-Exchange Complex	Equivalent to 45 mgs of Codeine Phosphate
Codeine Phosphate	15
~~Eudragit~~ EUDRAGIT ® L 100	10 to 100
Microcrystalline Cellulose	q.s*
Magnesium Stearate	5
Total	**500**

* Added to make remainder of weight.

[0137] The formula described above serves as a non-limiting example. Any active drug which is in the form of a salt, such as codeine, or dihydrocodeine, or hydrocodone can be incorporated as an ion-exchange resin complex.

Procedure:

[0138] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. ~~Amberlite~~ AMBERLITE ® IRP 69) to a codeine phosphate solution.

(2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

(3) Separate and dry the insoluble drug/resin complex.

(4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. ~~Eudragit~~

EUDRAGIT ® L 100, ~~Kollidon~~ KOLLIDON ® MAE, ~~Aquacoat~~ AQUACOAT® cPD) and dry the granules.

(5) Mill the granules, if needed.

(6) To the milled granules add the appropriate amount of microcrystalline cellulose and the remaining codeine phosphate in a V shaped blender and mix for 15 minutes.

(7) Add prescreened (sieve # 30) magnesium stearate to the above blend and mix for 3 minutes.

(8) Fill into appropriate capsules.

Example 18: Extended Release Suspension (Gel)

[0139] An extended release suspension (in the form of a gel) in accordance with the present invention which contains a codeine phosphate ion-exchange complex and promethazine hydrochloride is illustrated as follows (note that the codeine phosphate is used in a controlled release form since it has a shorter half-life than the promethazine hydrochloride):

Ingredients	**Amount / 5ml**
Codeine Phosphate Ion-Exchange Complex	Equivalent to 30 mgs of Codeine Phosphate
Promethazine HCl	25 mgs
~~Eudragit~~ EUDRAGIT ® L 100	0.2 to 2.8 grams
Glycerin	315 mgs
~~Polysorbate~~ POLYSORBATE 80	1.5 mgs

Carbomer (e.g., ~~Carbopol~~ CARBOPOL ® 974)	37.5 mgs
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Saccharin Sodium cryst., USP	0.1 mg
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Sodium Hydroxide	q.s.
Water	q.s

Procedure:

[0140] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. ~~Amberlite~~ AMBERLITE ® IRP 69) to a codeine phosphate solution.

(2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

(3) Separate and dry the insoluble drug/resin complex.

(4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. ~~Eudragit~~ EUDRAGIT ® L 100, ~~Kollidon~~ KOLLIDON ® MAE, ~~Aquacoat~~ AQUACOAT ® cPD) and dry the granules.

(5) Mill the granules, if needed.

(6) To an appropriate amount of water add the following ingredients and dissolve: promethazine hydrochloride, Carbomer (e.g., ~~Carbopol~~ CARBOPOL ® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

(7) Add milled granules.

(8) Add water to 95 % of final volume.

(9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

(10) Neutralize the solution to form a gel using a 1N sodium hydroxide solution. Add water to make final volume.

(11) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.

Example 19: Extended Release Suspension (Liquid)

[0141] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a codeine phosphate ion-exchange complex and promethazine hydrochloride is illustrated as follows:

Ingredients	**Amount / 5ml**
Codeine Phosphate Ion-Exchange Complex	Equivalent to 45 mgs of Codeine Phosphate
Promethazine HCl	25 mgs
~~Eudragit~~ EUDRAGIT ® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	100 mgs
Glycerin	740 mgs

Xylitol, NF	800 mgs
Sodium Citrate, USP	100 mgs
Saccharin Sodium cryst., USP,	0.1 mg
Sodium Benzoate	7.5 mgs
Citric Acid Monohydrate, USP	8.0 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s

Manufacturing process for 1000 L batch:

[0142] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. ~~Amberlite~~ AMBERLITE ® IRP 69) to a codeine phosphate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. ~~Eudragit~~ EUDRAGIT ® L 100, ~~Kollidon~~ KOLLIDON ® MAE, ~~Aquacoat~~ AQUACOAT ® CPD) and dry the granules. Mill the granules, if needed.

[0143] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50L of warm (about 45 °C), purified water. In another large stainless steel drum mix the silica, codeine phosphate ion-exchange complex, and promethazine hydrochloride until a uniform and consistent mixture is obtained. In a separate 1000 L

stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing codeine phosphate ion-exchange complex, and promethazine hydrochloride. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

Example 20: Extended Release Suspension (Liquid)

[0144] An extended release suspension (in the form of a liquid) in accordance with the present invention which contains a codeine phosphate ion-exchange complex, pseudoephedrine tannate and chlorpheniramine tannate is illustrated as follows:

Ingredients	**Amount / 5ml**
Codeine Phosphate Ion-Exchange Complex	Equivalent to 45 mgs of Codeine Phosphate
Pseudoephedrine Tannate	75.0
Chlorpheniramine Tannate	4.5
~~Eudragit~~ EUDRAGIT ® L 100	0.2 to 2.8 grams
Silica, colloidal anhydrous, NF	100 mgs
Glycerin	740 mgs
Xylitol, NF	800 mgs

Sodium Citrate, USP	100 mgs
Saccharin Sodium cryst., USP,	0.1 mg
Sodium Benzoate	7.5 mgs
Citric Acid Monohydrate, USP	8.0 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s

Manufacturing process for 1000 kg batch:

[0145] Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. ~~Amberlite~~ AMBERLITE® IRP 69) to a codeine phosphate solution. Stir the mix for 12 hrs to allow complete drug/resin complex formation. Separate and dry the insoluble drug/resin complex. Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. ~~Eudragit~~ EUDRAGIT ® L 100, ~~Kollidon~~ KOLLIDON ® MAE, ~~Aquacoat~~ AQUACOAT ® CPD) and dry the granules. Mill the granules, if needed.

[0146] In a suitably sized stainless steel vessel, dissolve saccharin sodium, sodium benzoate, citric acid, and sodium citrate in approximately 50L of warm (about 45 °C), purified water. In another large stainless steel drum mix the silica, codeine phosphate ion-exchange complex, pseudoephedrine tannate, and the chlorpheniramine tannate until a uniform and consistent mixture is obtained. In a separate 1000 L stainless steel tank equipped with a suitably sized homogenizer/disperser add about 100 L of purified water. With the homogenizer on, add the silica mixture containing codeine

phosphate ion-exchange complex, pseudoephedrine tannate, and the chlorpheniramine tannate. Add the previously prepared solution of saccharin sodium, sodium benzoate, citric acid, and sodium citrate to the 1000 L tank. Rinse the first vessel with about 2 L of water and transfer the rinsate to the 1000 L tank. Add the remaining ingredients and homogenize for 15 minutes.

Reference Example 1: Extended Release Suspension

[0147] An extended release suspension which contains a hydrocodone bitartrate ion-exchange complex, a dexchlorpheniramine maleate ion-exchange complex and a phenylepherine hydrochloride ion-exchange complex is illustrated as follows:

Ingredients	**Amount / 5ml**
Hydrocodone Bitartrate Ion-Exchange Complex	Equivalent to 8 mgs of Hydrocodone bitartarate
Dexchlorpheniramine Maleate Ion-Exchange Complex	Equivalent to 4mgs of Dexchlorpheniramine Maleate
Phenylepherine HCl Ion-Exchange Complex	Equivalent to 10 mgs of Phenylepherine HCl
~~Eudragit~~ EUDRAGIT ® L 100	0.2 to 2.8 grams
Glycerin	315 mgs
~~Polysorbate~~ POLYSORBATE 80	1.5 mgs

Carbomer (e.g.,~~Carbopol~~ CARBOPOL® 974)	15 mgs
Methyl Paraben	9 mgs
Propyl Paraben	1 mgs
Artificial Grape Flavor	5 mgs
FD&C Red # 40 Dye	0.5 mgs
Water	q.s

[0148] The formula described above serves as a non-limiting example. Any active drug which is in the form of a salt, such as codeine, or dihydrocodeine, or hydrocodone can be incorporated as an ion-exchange resin complex.

Procedure:

[0149] (1) Add the appropriate amount of sodium polystyrene sulphonate USP (e.g. ~~Amberlite~~ AMBERLITE ® IRP 69) to a codeine phosphate, dexchlorpheniramine maleate and phenylepherine HCl solution.

(2) Stir the mix for 12 hrs to allow complete drug/resin complex formation.

(3) Separate and dry the insoluble drug/resin complex.

(4) Granulate the drug/resin complex with a delayed release/enteric polymer (e.g. ~~Eugragit~~ EUDRAGIT ® L 100, ~~Kollidon~~ KOLLIDON ® MAE, ~~Aquacoa®t~~ AQUACOAT cPD) and dry the granules.

(5) Mill the granules, if needed.

(6) To an appropriate amount of water add the following ingredients and dissolve: Carbomer (e.g., ~~Carbopol~~ CARBOPOL ® 974), glycerin, polysorbate 80, methyl paraben, propyl paraben, artificial grape flavor, FD&C red # 40 dye.

(7) Add milled granules.

(8) Add water to make up to a final volume.

(9) Agitate at suitable rate to avoid settling of the suspension and maintain a homogeneous product mixture.

(10) Fill in suitable containers ensuring that the product is homogeneous throughout the filling operation.